

Trabalho Final

Mestrado Integrado em Medicina

Instituto de Anatomia Henrique de Vilhena

Cortical-Amygdala Volumetric Ratios Predict Onset of Symptoms of Psychosis in 22q11.2 Deletion Syndrome

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David Alves Berhanu

Orientado por:

Prof^a Doutora Lia Lucas Neto

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Resumo

O aparecimento de episódios psicóticos tem sido atribuído a alterações de regiões e circuitos corticais envolvidos na regulação de respostas emocionais. A disfunção destas redes corticais, envolvendo o córtex pré-frontal, córtex cingular e lobo temporal mesial, estão implicadas na fisiopatologia de sintomas psicóticos.

A síndrome de deleção 22q11.2 (22q11DS), também conhecida como síndrome velo-cardio-facial (VCFS) ou síndrome DiGeorge, é caracterizada pela deleção de uma região de 50 genes no locus 22q11.2 do braço longo do cromossoma 22. Em adição aos sintomas físicos, que incluem fendas palatinas, malformações cardíacas e facies atípico, indivíduos com 22q11DS desenvolvem frequentemente sintomas psiquiátricos, incluindo fobias e ansiedade generalizada, e cerca de 25-30% desenvolve perturbações psicóticas, primariamente esquizofrenia. Este aumento da predisposição para o desenvolvimento de episódios psicóticos realça a importância da determinação de biomarcadores e preditores de psicose nestes indivíduos, de forma a esclarecer a fase de desenvolvimento mais eficaz para a intervenção.

A disfunção cortical presente na esquizofrenia tem sido relacionada com alterações na morfologia cerebral, incluindo reduções volumétricas de regiões corticais e subcorticais. A disfunção de circuitos entre o cortex e a amígdala é considerada um factor de risco biológico para o desenvolvimento de episódios psicóticos. Esta associação levou-nos a propor uma correlação, em indivíduos com 22q11DS, entre a disfunção de áreas cerebrais responsáveis pela modulação de respostas emocionais e o aparecimento de perturbações psiquiátricas graves, especificamente sintomas psicóticos positivos. O presente estudo realizou a comparação de rácios entre o volume de regiões corticais e o volume da amígdala. Procurámos também averiguar a existência de uma relação entre estes rácios e o desenvolvimento de episódios psicóticos em jovens com 22q11DS.

Um grupo de 73 indivíduos com 22q11DS, 27 irmãos não afectados pela doença e 32 controlos foram incluídos no estudo e avaliados durante aproximadamente 12 anos. O diagnóstico de todos os participantes com 22q11DS foi confirmado por *fluorescence in situ hybridization* (FISH). Foram excluídos indivíduos do grupo de controlo que possuíssem história prévia e/ou um parente de primeiro grau com diagnóstico de doença bipolar ou perturbação psicótica. Os dados foram obtidos a partir de um estudo longitudinal de larga escala em que os participantes foram avaliados a cada 3 anos, em 4 *Timepoints*.

Neste estudo, foram analisados os dados imagiológicos da avaliação basal (*Timepoint 1*), e a frequência de sintomas psicóticos positivos no *Timepoint 4*. Foi extraído o volume de 34 regiões de interesse (*regions of interest - ROIs*) para cada hemisfério, com base no *Desikan FreeSurfer atlas*, bem como o volume da amígdala bilateralmente. A partir destes, foi calculado o rácio entre volume cortical/ volume da amígdala, resultando em 34 rácios por hemisfério, correspondentes às 34 ROIs. No *timepoint 4*, avaliação psiquiátrica foi conduzida por dois clínicos doutorados, tendo os diagnósticos sido determinados através da utilização da *Structured Interview for Prodromal Symptoms (SIPS)*. Apenas foram utilizados os scores de indivíduos com 22q11DS, dado que os restantes grupos não reportaram qualquer sintoma. Os scores foram obtidos através da escala: *Positive Symptom Subscale of the Scale of Prodromal Symptoms (SOPS)*.

Os rácios gerados no *Timepoint 1* para as 68 regiões de interesse volumétrico foram agrupadas em regiões lobares corticais: frontal, parietal, temporal, occipital e cingular. Foi realizada uma análise comparativa entre os diferentes grupos de estudo, com o objectivo de comparar o seu efeito no rácio entre o volume cortical e o volume da amígdala para cada região lobar. Com vista a eliminar potenciais enviesamentos, foram realizadas as respectivas correções para a idade e sexo na comparação de grupos de estudo. Em adição, foram ainda realizadas correções para comorbilidades psiquiátricas diagnosticadas e uso de medicação dos participantes, em análises separadas.

Posteriormente, foram testadas as associações entre os rácios corrigidos de volume ROI/amígdala, que apresentaram resultados com diferenças estatisticamente significativas entre grupos de estudo no *Timepoint 1*, e os scores de sintomas positivos (baseados no *SIPS Positive Symptom Subscale*) no *Timepoint 4*, em participantes com 22q11DS.

Os rácios avaliados no *Timepoint 1* revelaram diferenças estatisticamente significativas entre os rácios volume cortical e volume da amígdala de diferentes grupos de estudo. Estas diferenças verificaram-se em várias das 68 regiões cerebrais analisadas, incluindo regiões no lobo parietal, temporal, occipital e cingular. A análise dados revelou que, comparativamente com o grupo de irmãos não-afectados e com o grupo de controlo, os indivíduos com 22q11DS apresentaram rácios ROI/amígdala significativamente inferiores nas regiões rostral e caudal do córtex cingular anterior e no lobo parietal superior do hemisfério esquerdo. Algumas alterações estatisticamente significativas foram observadas, apenas comparativamente ao grupo de controlo, para regiões no lobo occipital. Todos os rácios significativamente inferiores verificados nos indivíduos com 22q11DS correspondiam a regiões corticais localizado no hemisfério esquerdo.

A análise da associação entre rácios de indivíduos com 22q11DS e o desenvolvimento de sintomas psicóticos revelou uma correlação inversa entre o rácio ROI/amígdala basal e o desenvolvimento de sintomas positivos SOPS no *Timepoint 4*. Correlações estatisticamente significativas foram observadas para rácios que envolviam a circunvolução cingular anterior, tanto a sua região rostral como a região caudal, o lóbulo parietal superior e o cuneus, no lobo occipital (esta última correlação apenas verificada para o grupo de controlo). Nestas regiões, os valores dos rácios ROI/amígdala indicam que valores basais inferiores estão associados a maiores scores na *Positive Symptoms Subscale of SOPS* no *Timepoint 4*.

Os resultados obtidos suportam a conclusão que estas são regiões chave no desenvolvimento de manifestações psiquiátricas em 22q11DS e que alterações nas regiões do lobo parietal, occipital e cingular, que diminuem o rácio entre o volume cortical e o volume da amígdala podem estar subjacentes, em parte, à fisiopatologia dos sintomas psicóticos positivos.

Palavras-chave: rácio volume cortical/amígdala; psicose; síndrome velo-cardio-facial; lobo cingular; insula.

Abstract

Dysfunction of cortical circuitry involving prefrontal cortex, cingulate gyrus and mesial temporal lobe has been implicated in the pathophysiology of psychotic symptoms. 22q11.2 deletion syndrome (22q11DS) is a neurogenetic disorder that comports a 25-fold increased risk of developing psychosis. Morphological changes in the neuroanatomy of this syndrome may represent a biological risk factor for the development of psychosis. The present study explored ratios between cortical volumes and the amygdala. We also explored relationships between these ratios and the eventual development of psychosis in youth with 22q11DS. A group of 73 individuals with 22q11DS and 27 unaffected siblings were followed every three years, at four timepoints. We analyzed baseline ratios between 34 bilateral FreeSurfer-generated cortical volumes and amygdala, and examined whether baseline cortical ratios predicted positive symptoms of psychosis 12 years later, at the 4th timepoint. Youth with 22q11DS demonstrated significantly smaller cortical volume-to-amygdala ratios in left anterior cingulate, occipital and parietal cortices. An increased risk of developing psychotic episodes in individuals with 22q11DS was associated with a lower cortical volume-to-amygdala ratio, suggesting that cortico-limbic circuitry may play an important role in emotional modulation and may underlie the pathophysiology of positive symptoms of psychosis.

Keywords: Cortical-amygdala ratios; psychosis; velocardiofacial syndrome; cingulate; insula.

O trabalho exprime a opinião do autor e não da FMUL.

Foi realizado no âmbito de um estágio de investigação internacional que teve lugar na Upstate Medical University, em New York.

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Introduction

22q11.2 deletion syndrome (22q11DS), also known as velo-cardio-facial syndrome (VCFS), is a neurogenetic disorder characterized by a deletion of a region containing over 50 genes on the long arm of the 22nd chromosome at the q11.2 locus. The most recent estimate of the prevalence of 22q11DS is 1:992 live births (1). Besides the physical symptoms, including cleft palate, heart defects and atypical facies, individuals with 22q11DS often develop psychiatric symptoms, including phobias and generalized anxiety. 25-30% develop psychotic disorders, primarily as schizophrenia (2; 3). This increased vulnerability for development of prodromal and full-blown psychosis highlights the importance of elucidating predisposing biomarkers and predictors of psychosis in these individuals, and by doing so, potentially determining the most effective developmental stage for intervention. It is thought that early recognition and intervention may be associated with a delayed or less severe clinical picture. (41)

The onset of psychotic episodes in individuals without 22q11DS has been attributed, in part, to the dysfunction of cortical regions and circuitry involved in the regulation of emotional responses. It has been considered that both dysfunction in the prefrontal cortices, as well as dysfunction in the amygdalae might be implicated in the pathophysiology of psychosis (4; 5). Moreover, the cortical dysfunction in schizophrenia has been related to changes in brain morphology, including volumetric reduction of cortical regions in the frontal and temporal lobe, as well as some subcortical regions, specifically the amygdala (4; 6). Some of these morphologic changes, such as cortical thinning within the cingulate and frontal cortices, have been further implicated in the modulation of emotional responses, and therefore may predict the development of psychotic episodes in patients with 22q11DS (7; 5; 8).

The amygdala is a group of nuclei located deep within the temporal lobe, at the anterior tip of the inferior horn of the lateral ventricle. It has been classically associated with the integration of information processing between prefrontal and temporal association cortices and the hypothalamus (42). This is achieved through cortical input fibers from the associations cortices and cingulate gyrus, which seem to impact amygdalae activation and through two major output fibers to the septal region and hypothalamus, the stria medularis pathway and the ventral amygdalofugal pathway, the latter also associated with an indirect output to the cortex (9; 42).

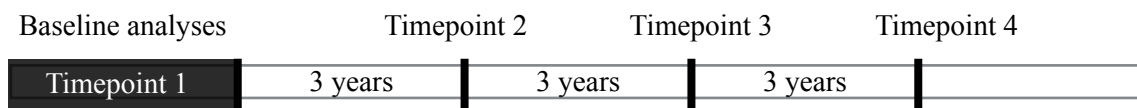
The anterior cingulate gyrus can be divided into a dorsal division, associated with cognitive processing and executive attention and a rostral division involved in the assessing of emotional information (9). The rostral anterior cingulate is connected with the amygdala and is thought to modulate its activity, therefore influencing the response to emotional stimuli. A rostral cingulate-to-amygdala pathway has been postulated to directly influence amygdala activation and associated the cingulate cortex signalling with an inhibitory role on the amygdala (9; 10). A link between dysfunction of the cingulate region and the appearance of positive symptoms of psychosis (specifically hallucinations) has been established, based on data collected by PET scans, structural and functional MRI and DTI studies, supporting the important role of the anterior cingulum on the development of psychotic symptoms (11).

Dysfunction of cortical-amygdala circuits is thought to be a biological risk factor for psychosis (12). It has been suggested that volumetric ratios between functionally coupled brain regions can represent a proxy of cortical-limbic circuitry underlying emotion regulation (12). Based on a cross-sectional, baseline study of a subset of the cohort analyzed here, we have previously reported that patients with 22q11DS exhibited smaller volumetric ratios of cortex to amygdala, which were associated with disruption of behavioral measures of anxiety, possibly representing a neuroanatomic substrate of emotional modulation difficulties in these individuals (13). This has led us to posit an association in 22q11DS between dysfunction of areas responsible for emotional modulation, such as the cingulate gyrus and prefrontal cortex, and the eventual onset of severe psychiatric disorders, and more specifically, positive symptoms of psychosis (14). Accordingly we hypothesized that: 1) individuals with 22q11DS would exhibit, at baseline, a reduced ratio between cortical volume of areas associated with emotional processing and the volume of the amygdala and 2) that the ratio would predict, up to ten years later, the presence of positive prodromal symptoms or overt psychosis in the same cohort, suggesting that a smaller ratio in children / early adolescents would represent a higher risk for psychosis in late adolescents or young adults with 22q11DS.

Methods

Participants

Participants included 73 individuals diagnosed with 22q11DS (38 males; mean age, 12.1 ± 2.23), 27 unaffected siblings (14 males; mean age, 12.6 ± 2.44) and 32 community controls (18 males; mean age, 12.99 ± 2.5). Participants with 22q11DS and their siblings were recruited from the Center for the Diagnosis, Treatment and Study of VCFS at SUNY-Upstate Medical University. The diagnosis of all the participants with 22q11DS had been confirmed before enrollment in the study, by fluorescence in situ hybridization (FISH). The detailed recruitment methods have been described previously (13). Community controls were recruited from local public schools. Exclusion criteria for all participants in the study included seizure disorder, fetal exposure to alcohol or drugs, parent-reported elevated lead levels or birthweight under 2500 grams, loss of consciousness lasting longer than 15 minutes, paramagnetic implants, or orthodontic braces. Additionally, community controls were also excluded if they had a personal history of and/or a first-degree relative with a diagnosis of bipolar disorder or psychosis.



Data were acquired from a large-scale longitudinal study at the Upstate Medical University of New York investigating risk factors for psychosis in 22q11DS. All participants were asked to return after the initial analyses for follow-up at three subsequent timepoints. However for the present report, we analyzed baseline imaging data (Timepoint 1), and the frequency of positive symptoms of psychosis at Timepoint 4, approximately 12 years later. Mean age of participants with 22q11DS at Timepoint 1 was 12.1 ± 2.2 years, and at Timepoint 4 was 21.2 ± 1.7 years; the mean age of controls and siblings at Timepoint 1 was 12.9 ± 2.5 ; 12.6 ± 2.4 years, and at Timepoint 4 was 20.2 ± 2.7 ; 20.5 ± 2.6 , respectively. At baseline, 15 individuals with 22q11DS were currently being treated with one or more antipsychotic, mood stabilizer, antidepressant, antianxiety, or stimulant medication at the time of image acquisition. Two siblings were being treated with either a stimulant or antidepressant, and 8 community controls were being treated with a psychotropic medication, primarily stimulants. Because the present study aims to investigate cortical-amygdalar volumes as biomarkers of psychotic symptoms in a 12-year time span, we allowed the enrollment of siblings and controls who

had a diagnosis of attention-deficit/hyperactivity disorder as this disorder has not been determined to be a biomarker for psychosis (13). All participants provided informed consent/assent, and the Institutional Review Board of the Upstate Medical University approved all study protocols.

Procedures

i) Image acquisition

Imaging data were acquired on a 1.5-T Philips Intera scanner (Philips Medical Systems, Best, The Netherlands) in the axial plane utilizing following T1-weighted inversion recovery turbo gradient echo TFE) 3-D pulse sequence: TE = 4.6ms; TR = 20ms; two repetitions; matrix size 256 x 154; FOV= 24cm; multishot = 32; TFE pre-inversion recovery = 394ms; 1.5mm slice thickness; voxel size = 1.0 mm x 1.0 mm x 1.5 mm.

ii) Imaging data processing

Raw MRI data was imported into BrainImage software (available from the Center for Interdisciplinary Brain Sciences Research, Stanford University). After creating an isotropic brain image, we subsequently performed initial intensity correction, and generated a brain mask for the removal of non-brain tissue and skull-stripping. The images were aligned along the anterior-posterior commissure and then resampled into isotropic voxels (0.9375 mm^3) using a cubic spline interpolation transformation in 3DSlicer (www.slicer.org) (15). Additional details regarding image processing can be found in McCarthy et al., 2015. Utilizing the FreeSurfer image analysis suite (version 5.1.0, <https://surfer.nmr.mgh.harvard.edu>), an automated surface-based reconstruction and volume-based subcortical segmentation processing pipeline was implemented to acquire measures of volume. Briefly, this processing stream included motion correction, registration of images to Talairach space, intensity normalization, removal of non-brain matter, and cortical reconstruction and segmentation of white matter and subcortical structures. As noted above, the current set of analyses is based on cross sectional datasets acquired at baseline from a longitudinal study of biomarkers for psychosis. Accordingly, for the analyses described below, these cross-sectional datasets were not subject to the manual interventions / editing entailed in our FreeSurfer longitudinal pipeline. Notably, however, a recent study by McCarthy and colleagues investigated the impact of edited versus unedited FreeSurfer 1.5 Tesla data on cortical volumes. With the exception of white matter volumes, no significant differences were observed in cortical and subcortical volumes.

Accordingly, after final reconstruction was carried out, as described in prior publications (16,17,18), we extracted volume for cortical regions of interest (ROIs) based on the Desikan FreeSurfer atlas (19) for each hemisphere, as well as bilateral amygdalar volumes. We then calculated cortical-volume-to-amygdala ratios, resulting in 34 ROI-based ratios per hemisphere.

iii) Psychiatric and Neuropsychological Assessment

Psychiatric diagnoses were derived from the Structured clinical interview for DSM-IV-TR axis I disorders (SCID; 20). Diagnoses of prodromal symptoms at Timepoint 4 were determined using the Structured Interview for Prodromal Syndromes [SIPS; (21)]. Since controls and siblings did not report prodromal symptoms, only scores from individuals with 22q11DS were used for these analyses. Scores were taken from the Positive Symptom Subscale of the Scale of Prodromal Symptoms [SOPS]. Two doctoral-level clinicians (KMA and WF) conducted the interviews. Interrater reliability, based on five consecutive audio-taped interviews, and calculated with the intraclass correlation coefficient was 0.91. Separate interviews were conducted with the participant and his / her parent: final scores were based on the more severe rating derived from the SOPS. As noted above, the psychiatric assessment, and scores used in this report were obtained at Timepoint 4 to provide the most accurate prodromal status of the participant. However, when Timepoint 4 data were not available, scores from Timepoint 3 (N=20) were used. Analyses of variance (ANOVAs) were conducted to rule out any differences in age, gender, and ROI/amygdala ratios between groups who only had psychiatric data from Timepoint 3 and those who had data from Timepoint 4. Since we did not find any significant between-group differences after correction for multiple comparisons, we combined groups for subsequent analyses.

To determine whether any neuropsychological measures corresponded with the conversion of psychosis at Timepoint 4, we tested associations between general intellectual functioning utilizing full scale IQ scores from the Wechsler Adult Intelligence Scale, Third Edition (WAIS; 22). We also conducted computer-generated paradigms including the visuo-spatial working memory test (VSPAN; 23), utilizing summed scores of both the VSPAN forward and backward tests, and the Penn Emotional Recognition Task (24) using the total correct score to test associations with cortical volume/amygdala ratios. Neuropsychological assessments and computer paradigms were completed by a trained, doctoral-level psychologist.

iv) Statistical analyses

Cortical volume-to-amygdala ratios were generated for all 68 volumetric regions of interest (ROIs) generated by FreeSurfer (34 ROIs per hemisphere). Cortical volumes were then combined with subcortical volumes from the bilateral amygdala for analyses. Initially, ratios were grouped into their respective cortical lobar regions: frontal, parietal, temporal, occipital, and cingulate. Multivariate analyses of variance (MANOVAs) were conducted in SPSS (v23) to determine the extent to which the three study groups differed in mean ROI-to-amygdala ratios within each lobar region. After determining that Wilks' Lambda values were significant for each lobar region ($p < 0.001$), follow-up analyses of variance (ANOVAs) were conducted to ascertain the effect of study group on individual ROI-to-amygdala ratios within each lobar region. To rule out potential age and gender effects (12) in our between-group analyses, we included age and gender as covariates in the models. In addition, we covaried for comorbid psychiatric diagnoses, and medication usage, in separate analyses.

We then tested the associations between the corrected ROI-to-amygdala ratios that significantly differentiated study groups at baseline, and the Timepoint 4 positive symptom scores (based on the SIPS Positive Symptom subscale) in participants with 22q11DS. Since the SIPS produces a count variable, and a relatively large proportion of individuals with 22q11DS had scores of zero on the SIPS positive symptom subscale, we used the zero-inflated poisson (ZIP) regression analysis to test these associations. Only FDR-corrected associations ($p^{FDR} < 0.05$) based on these regression analyses are reported below. To test associations between neuropsychological paradigms and cortical/amygdala ratios, Pearson R correlations were conducted, and FDR-corrected to correct for multiple comparisons.

In the analyses described above, the SIPS Positive Symptom subscale was treated as a dimensional variable. We also treated this subscale as a categorical variable, by dividing the sample of individuals with 22q11DS into those with (N=15) and without (N=58) positive prodromal symptoms, based on a threshold of a score of 3 or higher on any of the five items that comprised the SIPS Positive Symptom subscale (21). We then conducted t-tests to compare the corrected ROI-to-amygdala ratios that had significantly differentiated the study groups at baseline.

Results

Group differences in cortical volume/amygdala ratios

Baseline ratios at timepoint 1 revealed statistically significant, Bonferroni-corrected ($p < 0.005$) differences in volume to amygdala ratios between study groups in multiple brain regions including the cingulate, parietal, temporal and occipital lobe (Table 1; Supplementary Figure 1; Supplementary Table 1). Relative to controls (but not siblings), individuals with 22q11DS exhibited significantly smaller volume to amygdala ratios mainly in the left hemisphere: precuneus ($F=15.183$, $p < 0.001$) of the parietal lobe; in the superior temporal gyrus ($F=6.897$, $p = 0.001$), fusiform gyrus ($F=6.533$, $p = 0.002$), and transverse temporal gyrus ($F=7.023$, $p = 0.001$) of the temporal lobe; in the lateral occipital ($F=6.368$, $p = 0.002$), lingual ($F=8.889$, $p < 0.001$), and cuneus ($F=11.058$, $p < 0.001$) of the occipital lobe. Relative to both controls and siblings, participants with 22q11DS displayed significantly smaller volume to amygdala ratios in the rostral and caudal anterior cingulate ($F=17.112$, $p < 0.001$; $F=17.533$, $p < 0.001$, respectively) subregions of the cingulate gyrus; and in the superior parietal lobe ($F=17.907$, $p < 0.001$). Interestingly, we observed larger volume to amygdala ratios in the insula in individuals with 22q11DS compared to both controls and siblings ($F=7.583$, $p = 0.001$). Relative to siblings only, participants with 22q11DS also displayed increased volume to amygdala ratios in the right temporal pole ($F=6.232$, $p = 0.003$). With the exception of the right temporal pole – amygdala ratio, these significant cortical – amygdala ratios were all located in the left hemisphere. No significant differences in volume to amygdala ratios were observed between controls and siblings.

As noted above, ANOVA's were also conducted with the inclusion of comorbid psychiatric diagnosis and medication usage as covariates. Neither comorbid psychiatric diagnoses nor medication usage accounted for a significant portion of the variance. Moreover, the main effect of study group remained highly significant for parietal, occipital, cingulate and insula ratios. However, for three of the temporal lobe ratios (superior temporal, fusiform and transverse temporal) significance for the main effect of study group dropped to p-values between 0.01 and 0.02 (thus no longer passing correction for multiple comparisons). Accordingly, comorbid diagnoses and medication usage appeared to moderate group differences in cortical temporal-to-amygdala ratios.

Cortical Volume Ratios and Neuropsychological Variables

Correlations between cortical volume ratios that significantly distinguished the study group, and FSIQ, emotion facial recognition, and visual working memory did not pass correction for multiple comparisons.

Cortical Volume Ratios and Psychiatric Symptoms

As noted above, we conducted ZIP regression analyses in individuals with 22q11DS for all the ROI-to-amygdala ratios that significantly differentiated individuals with 22q11DS and siblings.

After correction for multiple comparisons ($p_{\text{FDR}} < 0.05$), we observed inverse correlations between baseline ROI-to-amygdala ratios and the SOPS positive symptoms score at Timepoint 4 9 (Table 2). Statistically significant correlations were observed for ratios that consisted of the anterior cingulate, both rostral ($\beta = -0.53$; $p = 0.014$) and caudal ($\beta = -0.95$; $p = 0.0175$) regions, superior parietal lobule ($\beta = 0.12$; $p = 0.014$) and occipital cuneus ($\beta = 0.40$; $p = 0.0448$) and occipital pericalcarine ($\beta = 0.71$; $p = 0.0175$) regions, indicating that lower baseline values for these ratios were associated with higher scores on the Positive Symptoms Subscale of the SOPS at Timepoint 4.

Comparisons of the same FDR-corrected, baseline ratios between individuals with and without scores equal to or greater than 3 on at least one item of the SOPS Positive Symptoms Subscale did not yield significant results.

Discussion

We hypothesized that: 1) relative to controls and siblings, individuals with 22q11DS would exhibit reduced baseline ratios between cortical volume of areas associated with emotional processing and the volume of the amygdala and; 2) that baseline ratios would predict positive symptoms of psychosis at Timepoint 4 in individuals with 22q11DS, such that a smaller ratio would predict a higher risk for psychosis. Both hypotheses were confirmed by our analyses. Interestingly, the majority of study group differences was driven by differences between individuals with 22q11DS and controls, as opposed to siblings, suggesting the potential role of familial influence on the anatomic network that underlies emotion processing. The cortical- amygdala ratios that showed significant differences between controls and individuals with 22q11DS were based in parietal, temporal, occipital lobes, and insula and cingulate. Study group differences in the insula-amygdala ratio are consistent with previous studies that have included insula-amygdala connectivity in the functional connectivity network that underlies emotion processing in typical individuals (25). Reciprocal connections between the cingulate and the amygdala have also been well-documented (26, 27). Moreover, in a primate model, projections have been shown to be more numerous in the cingulate-to-amygdala direction relative to the opposite direction (28), providing anatomical support for the top-down regulation of amygdala-mediated emotional responses that numerous functional brain imaging studies (29,30; see review by 31) have suggested. Similarly, altered prefrontal-amygdala coupling has been reported in individuals with psychosis (32) as well as psychosis-proneness (33).

Reduced cortical to amygdala ratios are consistent with findings of reduced volumes in the anterior cingulate, fusiform, precuneus, superior parietal, as well as reported findings of increased volumes in the insula (34). Volumetric reductions in these regions have been found to be driven by reductions in surface area, and interestingly, increased cortical thickness has been determined to drive larger insular volumes in 22q11DS (34). These findings further support the notion of delayed or disrupted neurodevelopment in 22q11DS due to reduced gene dosage in the 1.5-megabase minimal critical deleted region in a mouse model of 22q11DS (35). Disruption of basal progenitors and atypical distribution of interneurons are thought to play a significant role in the disruption of

cortical neurogenesis and interneuron migration, and ultimately delay in neurodevelopment in 22q11DS, leading to neurocognitive deficits and vulnerability for psychosis (35; **2012**).

Connections between posterior regions of the brain and the amygdala have not been as extensively studied as prefrontal / cingulate-amygdalar connections. However, reciprocal connections between amygdala and both superior temporal gyrus and occipital lobe have been described in non-human primate studies (Amaral and Price, 1984). Although functional imaging studies have not reported strong functional connections between amygdala and occipital lobe (36), the occipital lobe has been implicated in psychosis (8), and the visual processing of emotional situations and faces has been shown to be dependent upon amygdalar activation (37). These anatomic (8) and functional (37) imaging studies suggest that the visual cortex may also be involved in the modulation of the emotional response.

Our analysis revealed a negative correlation between cortico-amygdala ratios and SOPS Positive Symptom scores, indicating that a lower cortical volume/amygdala ratio in late childhood / early adolescence is associated with an increased risk of developing psychotic positive symptoms in late adolescence and young adulthood. These findings support the conclusion that these are key regions in the development of psychiatric manifestations in 22q11DS and that abnormalities in cingulate, parietal and occipital regions that decreases the cortical-to-amygdala volume ratio may underlie, in part, the pathophysiology of positive symptoms of psychosis. Moreover, this study supports the notion that volumetric ratios between brain regions known to be functionally connected can represent an anatomic proxy of cortical-limbic circuitry as it pertains to individuals with 22q11DS.

Our results should be considered in light of the limitations of the study. Although we observed significant associations between ROI-to-amygdala ratios and prodromal symptoms when we treated the SOPS positive symptom scale as a dimensional variable, we did not detect significant differences between 22q11DS-affected participants with and without prodromal / overt psychosis when the SOPS was treated as a categorical variable. Significant results from a direct comparison between those with and without prodromal / overt psychosis would have provided more definitive evidence for the link between alterations in cortico-limbic circuitry and risk for psychosis. Most likely, our sample of individuals with prodromal / overt psychosis was not large enough to detect those differences. Accordingly, the association we observed between alterations in cortical-limbic

anatomic circuitry during late childhood / early adolescence and the presence of symptoms of psychosis in late adolescence / early adulthood must be viewed as preliminary evidence that cortico-limbic anatomy may be a compelling biological marker for risk for psychosis. Future studies with larger samples are necessary to confirm whether these findings can pave the way for the identification, and early intervention of those youth with 22q11DS who are at highest risk for the development of prodromal psychosis.

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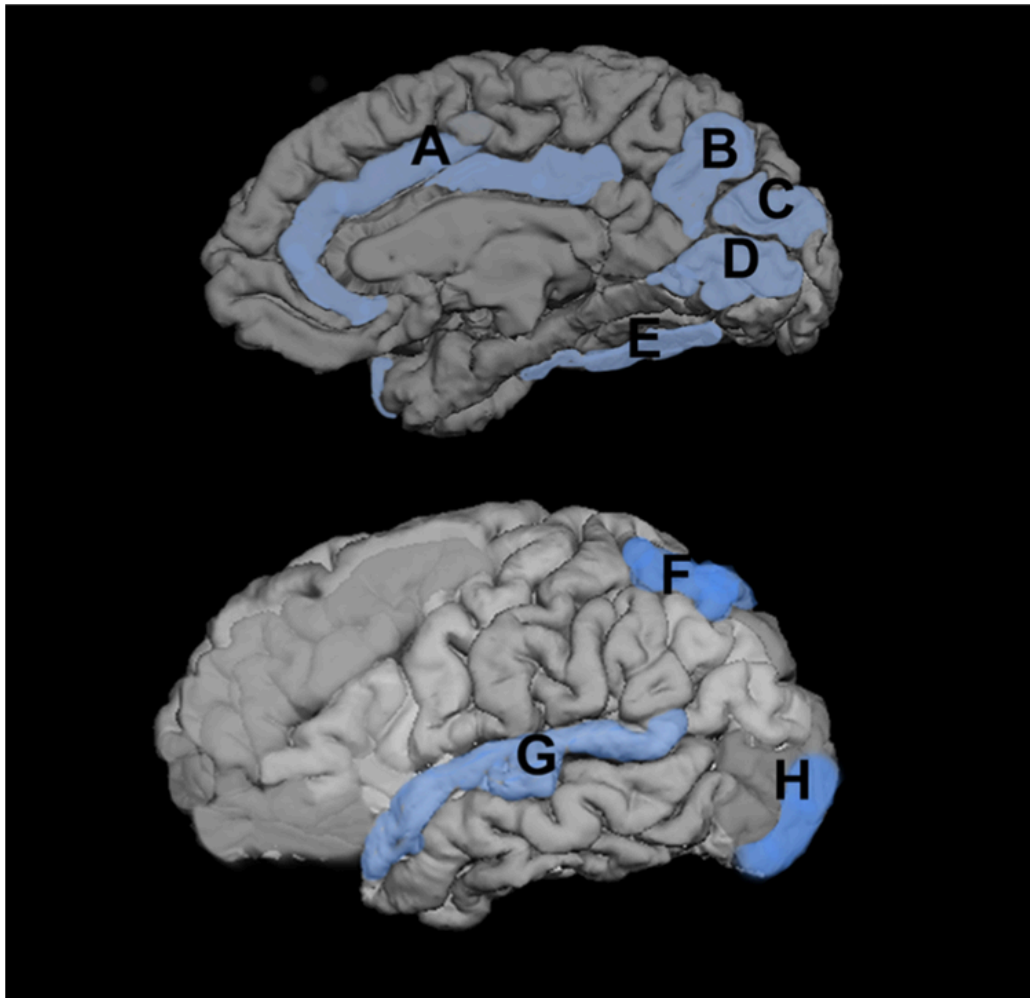
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Supplementary Figure 1. This image depicts baseline cortical volume – to – amygdala ratios that significantly differentiated individuals with 22q11DS from community controls and, in several instances, unaffected siblings. Labels that are in boldface also predicted to symptoms of psychosis approximately 12 years later.

- A. Rostral and caudal anterior cingulate**
- B. Precuneus
- C. Cuneus**
- D. Lingual gyrus
- E. Fusiform gyrus
- F. Superior parietal lobe**
- G. Superior temporal gyrus
- H. Lateral occipital gyrus

Table 1

Results of MANOVAs comparing cortico-amygdala ratios between individuals with 22q11DS, siblings and controls, with age and gender included as covariates.

Lobe	Wilks' Lambda	p-value	Region	F (df)	p-value / Eta ²	Post-hoc Comparisons
Parietal	0.440	< 0.0001	LH superior parietal	17.907 (2, 127)	< 0.0001 / .22	22q < C, S
			LH precuneus	15.183 (2, 127)	< 0.0001 / .19	22q < C
Temporal	0.550	< 0.0001	LH superior temporal	6.897 (2, 127)	0.001 / .10	22q < C
			LH fusiform	6.533 (2, 127)	0.002 / .09	22q < C
			LH transverse temporal	7.023 (2, 127)	0.001 / .10	22q < C
			RH temporal pole	6.232 (2, 127)	0.003 / .09	22q > S
Occipital	0.774	0.011	LH lateral occipital	6.368 (2, 127)	0.002 / .09	22q < C
			LH lingual	8.889 (2, 127)	< 0.0001 / .12	22q < C
			LH cuneus	11.058 (2, 127)	< 0.0001 / .15	22q < C
Cingulate	0.683	< 0.0001	LH rostral anterior cingulate	17.112 (2, 127)	< 0.0001 / .21	22q < C, S
			LH caudal anterior cingulate	17.533 (2, 127)	< 0.0001 / .22	22q < C, S
Insula	0.889	0.005	LH insula	7.583 (2, 127)	0.001 / .11	22q > C, S

Note. Only ratios that were significant, after Bonferonni correction, in planned, follow-up comparisons are included.

LH = left hemisphere; RH = right hemisphere; 22q = 22q11DS. C = Controls; S = Siblings.

Table 2

Results from ZIP regression analysis to determine association between cortico-amygdala ratios and scores on the Positive Symptom Subscale of the Scale of Prodromal Symptoms*

Lobe	Ratio	z	p-value	p-value, FDR-corrected
Parietal	LH superior parietal	3.14	0.002	0.014
	LH precuneus	1.6	0.109	
Temporal	LH superior temporal	1.58	0.114	
	LH fusiform	-1.35	0.178	
	LH transverse temporal	-0.8	0.422	
	RH temporal pole	-0.73	0.464	
Occipital	LH lateral occipital	1.75	0.08	
	LH lingual	0.44	0.657	
	LH cuneus	2.42	0.016	0.0448
Cingulate	LH rostral anterior cingulate	-3.22	0.001	0.014
	LH caudal anterior cingulate	-2.82	0.005	0.0175
Insula	LH insula	0.41	0.679	

Note. ZIP = Zero-inflated Poisson. lh= left hemisphere. rh = right hemisphere. FDR = False Discovery Rate.

*FDR-corrected, $p < 0.05$.

Supplementary Table 1.

Means and standard deviations of all cortical-to-amygdala volumetric ratios, by study group

<u>Cortical Region</u>	Controls N = 73		Siblings N = 32		22q11DS N = 27	
	Mean	SD	Mean	SD	Mean	SD
LH banks superior temporal sulcus	2.16	0.39	2.04	0.40	1.97	0.46
RH banks superior temporal sulcus	1.99	0.45	1.85	0.39	2.00	0.93
LH caudal anterior cingulate	1.26	0.40	1.25	0.31	0.95	0.24
RH caudal anterior cingulate	1.45	0.32	1.37	0.33	1.28	0.54
LH caudal middle frontal	5.31	1.21	5.03	0.97	5.23	1.04
RH caudal middle frontal	5.04	1.38	4.76	1.09	5.37	2.75
LH cuneus	2.22	0.55	2.05	0.39	1.87	0.38
RH cuneus	2.24	0.50	2.14	0.36	2.03	0.68
LH entorhinal	1.44	0.34	1.51	0.26	1.49	0.42
RH entorhinal	1.37	0.32	1.31	0.33	1.39	0.50
LH fusiform	7.99	1.50	7.43	1.25	7.22	1.26
RH fusiform	7.15	1.31	6.78	1.18	7.06	2.47
LH inferior parietal	10.40	2.02	9.35	1.95	10.26	1.82
RH inferior parietal	12.53	2.43	11.99	2.76	13.00	5.08
LH inferior temporal	8.33	1.84	8.13	1.04	7.59	1.45
RH inferior temporal	8.11	1.58	7.73	1.01	8.06	2.68
LH isthmus cingulate	2.10	0.44	2.02	0.40	2.00	0.43
RH isthmus cingulate	1.87	0.35	1.85	0.51	1.90	0.61

LH lateral occipital	8.66	1.94	8.12	1.51	7.81	1.24
RH lateral occipital	9.04	1.71	8.47	1.76	8.46	2.72
LH lateral orbito frontal	6.06	1.16	5.94	0.84	6.28	0.91
RH lateral orbito frontal	5.78	1.06	5.80	0.95	6.17	1.46
LH lingual	5.08	0.99	4.79	0.85	4.47	0.80
RH lingual	4.95	1.10	4.73	0.91	4.58	1.55
LH medial orbito frontal	4.52	0.85	4.32	0.55	4.60	0.77
RH medial orbito frontal	4.28	0.86	4.14	0.57	4.51	1.35
LH middle temporal	8.61	1.90	8.44	1.02	8.25	1.52
RH middle temporal	9.75	1.89	9.13	1.58	10.11	3.61
LH parahippocampal	1.77	0.51	1.60	0.21	1.61	0.31
RH parahippocampal	1.49	0.25	1.51	0.34	1.49	0.53
LH paracentral	2.65	0.55	2.58	0.42	2.46	0.52
RH paracentral	2.90	0.68	2.90	0.44	2.87	1.43
LH pars opercularis	4.00	0.80	3.68	0.61	3.98	0.97
RH pars opercularis	3.32	0.75	3.11	0.49	3.63	1.47
LH pars orbitalis	1.78	0.43	1.81	0.30	1.89	0.36
RH pars orbitalis	2.14	0.50	1.98	0.42	2.32	0.82
LH pars triangularis	3.05	0.69	2.87	0.59	2.95	0.55
RH pars triangularis	3.60	0.92	3.35	0.60	3.49	1.36
LH pericalcarine	1.46	0.40	1.37	0.28	1.32	0.27
RH pericalcarine	1.53	0.41	1.51	0.32	1.51	0.66

LH postcentral	8.02	1.38	7.54	1.37	7.52	1.24
RH postcentral	7.28	1.38	6.69	1.50	7.04	2.64
LH posterior cingulate	2.36	0.37	2.36	0.45	2.18	0.37
RH posterior cingulate	2.36	0.56	2.26	0.36	2.36	0.93
LH precentral	10.18	1.70	9.81	1.53	10.68	1.77
RH precentral	9.92	1.89	9.58	1.32	11.13	4.38
LH precuneus	7.86	1.54	7.11	1.02	6.81	1.13
RH precuneus	7.70	1.59	7.21	1.31	7.23	2.49
LH rostral anterior cingulate	1.98	0.45	1.95	0.39	1.56	0.38
RH rostral anterior cingulate	1.67	0.41	1.59	0.43	1.49	0.50
LH rostral middle frontal	12.82	2.28	12.71	1.77	12.18	2.11
RH rostral middle frontal	13.44	2.55	12.88	2.77	13.20	4.80
LH superior frontal	18.60	3.41	17.73	1.83	17.69	2.72
RH superior frontal	17.96	3.15	17.40	2.22	18.23	6.61
LH superior parietal	10.57	2.43	10.44	1.74	9.02	1.70
RH superior parietal	10.32	1.98	10.00	1.86	9.55	3.48
LH superior temporal	9.52	1.73	8.86	1.36	8.55	1.44
RH superior temporal	9.01	1.67	8.57	1.25	8.90	3.77
LH supramarginal	9.27	1.69	8.55	1.54	9.01	1.57
RH supramarginal	8.52	1.43	7.93	1.75	8.52	3.30
LH frontal pole	0.76	0.21	0.74	0.15	0.76	0.18
RH frontal pole	0.98	0.30	0.90	0.23	1.08	0.44
LH temporal pole	1.93	0.38	1.76	0.30	1.97	0.40
RH temporal pole	1.55	0.36	1.41	0.29	1.77	0.55

LH transverse temporal	0.89	0.22	0.84	0.17	0.77	0.18
RH transverse temporal	0.71	0.18	0.65	0.11	0.67	0.31
LH insula	5.15	0.90	4.91	0.56	5.59	0.79
RH insula	5.27	0.96	5.12	0.64	6.22	2.86